REMARKS

Claims 1-14 are pending and under consideration. With this Amendment, claims 1, 10, 11 and 12 are being amended, claim 9 is being canceled without prejudice and claims 15 and 16 are being newly added. Thus, after entry of this Amendment, claims 1-8 and 10-16 are pending and under consideration. The various amended and new claims, as well as the rejections raised in the Office Action, are discussed in more detail, below.

THE AMENDMENTS OF THE CLAIMS

Claim 1 has been amended to focus the compositions on embodiments in which the outer layer of the microparticle shell is composed of a cross-linked amphipathic protein and the inner layer is composed of a synthetic biodegradable polymer. Support for the amendments is found through the disclosure as originally filed, including, for example, page 6, lines 4-7 (cross-linked protein outer shell layer) and page 5, lines 32-33 (synthetic biodegradable polymer inner shell layer). The amendments of claims 10, 11 and 12 either correct errors in antecedent basis introduced by the amendment of claim 1, or correct obvious errors in grammar.

New claims 15 and 16 focus on embodiments of the compositions of claims 1 and 12, respectively, in which the microparticles comprising the compositions do not contain a drug. Such embodiments, which are useful for diagnostic ultrasound imaging, are described throughout the application or originally filed, as well as in the working Examples.

No new matter is introduced by the amendments of claims 1 and 10-12 and new claims 15 and 16. Accordingly, entry into the application is requested.

REJECTION UNDER 35 U.S.C. § 103(a)

Claims 1-14 stand rejected under 35 U.S.C. § 103(a) as being allegedly obvious over EP 0 458 745 to Bichon *et al.* ("Bichon *et al.*") in view of U.S. Patent No. 4,466,442 to Hilmann *et al.* ("Hilmann *et al.*") and further on view of WO 91/06287 to Bernstein *et al.* ("Bernstein *et al.*"). Applicants traverse the rejection.

Instant independent claim 1 is directed to a composition comprising a plurality of microparticles and a sugar. The microparticles comprise a shell enclosing a gas-filled hollow core. The shell comprises two layers: an outer layer composed of a cross-linked amphiphilic protein and an inner layer composed of a synthetic biodegradable polymer.

Instant independent claim 10 is directed to a composition comprising a plurality of microparticles, glycine and polyethylene glycol 3350. The microparticles comprise shells enclosing a gas-filled hollow core. The shells comprise an inner layer composed of polylactide and an outer layer composed of glutaraldehyde cross-linked human serum albumin.

The Bichon *et al.* reference is relied upon as teaching compositions comprising microballoons[1] filled with air or gas for use in ultrasound echography. As correctly noted by the Patent Office, Bichon *et al.* do not teach the use of nitrogen gas, or microballoons having a membrane composed of two layers of polymers.

The Hilman *et al.* reference is relied upon as teaching nitrogen as a preferred gas for incorporation into microparticles for use in ultrasound echography.

The Bernstein *et al.* reference is relied upon as teaching layering of polymers to form microparticles of various sizes, durability and release properties.

The crux of the rejection appears to be rooted in the contention that these references, in combination, render microparticles having a multilayered shell, as recited in instant claims 1 and 10 obvious:

> It would have been obvious to the person of ordinary skills in the art at the time of the invention to produce a multilayered microparticle comprising the polymers of Bichon *et al.*, to fill the cores of the microparticles with nitrogen ... to arrive at the instantly claimed compositions.

Office Action at page 4. Applicants disagree.

As an initial matter, it is noted that the rejection is based upon a misunderstanding of the Bernstein *et al.* reference. In support of the rejection, the Patent Office states:

> Bernstein *et al.* teach that the same polymers and proteins exemplified by Bichon *et al.* can be layered to form multilayered microparticles (pp. 13-15).

Office Action at page 4 (emphasis supplied). This is not the case.

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[1] In the office Action, the Patent Office refers to the microballoons of Bichon *et al.* as "microparticles." Since the Bichon *et al.* reference uses the term "microballoons," that term is used herein.

The Bernstein *et al.* reference concerns biodegradable, protein microspheres for *in vivo* release of biologically active agents (*see e.g.*, Abstract). The protein microspheres are solid (*see, e.g.*, Bernstein *et al.* page 7, lines 6-8). The biologically active agents are released from the microspheres by "diffusion from and/or degradation of the microsphores," Bernstein *et al.* at page 4, lines 25-29.

Proteins useful for forming the microspheres are taught at page 8, line 30 through page 9, line 18. The only proteins specifically taught are hydrophobic proteins such as prolamines (*e.g.*, zein), collagen, casein and keratin (*see, e.g.*, page 8, line 31 and claim 3 specifying that collagen, casein and keratin are hydrophobic proteins).

The passage of the Bernstein *et al.* reference relied upon by the Patent Office – pages 13-15 – is directed to "composite microspheres." According to the authors, "[p]roteins can be combined with non-protein polymers to form composite microspheres," Bernstein *et al.* at page 13, lines 22-23. Examples of suitable polymers include synthetic polymers such as PLA, PGA, PLA/PGA copolymers and others. However, contrary to the assertion of the Patent Office, this passage does not teach that the same polymers and proteins exemplified by Bichon *et al.* can be layered to form multilayer microparticles. It is clear from the context of the passage that the proteins comprising the composite microspheres are the proteins specifically taught in the Bernstein *et al.* reference as being useful in the disclosed protein microspheres, *i.e.*, hydrophobic proteins such as prolamines (*e.g.*, zein), collagen, casein and keratin.

The fact that Bernstein *et al.*, specifically mention some of the same synthetic polymers mentioned by Bichon *et al.* does not mean that Bernstein *et al.* teach that all polymers and proteins mentioned in Bichon *et al.* are useful in their disclosed composite microspheres. The entirety of the Bernstein *et al.* reference concerns protein microspheres, and the authors explicitly teach which proteins can be used to make their microspheres. The only proteins mentioned are hydrophobic proteins (see, in addition to the passages cited above, all fifteen working Examples, which are directed to protein microspheres composed of the hydrophobic prolamine zein). The Patent Office has no basis to conclude that other proteins, and in particular the proteins mentioned in the Bichon *et al.* reference (although not specifically stated, presumably cross-linked albumin), could be used in the polymer-protein composite microspheres of Bernstein *et al.*

The Patent Office contends that the person of ordinary skill "would have been motivated to layer the polymers of Bichon *et al.* because Bernstein *et al.* teach that by layering the polymers, the size, durability and release properties of microspheres can be modulated," Office Action at page 4, ¶ 12. Applicants request the Patent Office to identify where in the Bernstein *et al.* reference this concept is

taught. Applicants have reviewed the document and are unable to find this teaching. To the extent the Patent Office is relying on the disclosure at page 14, line 19 through Page 15, line 2, Applicant submits it is inapposite. These paragraphs relate to the properties of matrices comprising mixtures of proteins and polymers, not layers (see, *e.g.*, page 14, lines 29-31).

Independent claim 1 requires that the outer layer of the microparticle shell be composed of a cross-linked amphiphilic protein. Dependent claim 10 requires that the cross-linked protein be a cross-linked human serum albumin. Independent claim 12 is directed to a composition comprising microparticles in which the outer layer of the shell is composed of glutaraldehyde cross-linked human serum albumin. The Patent Office has provided no reasoning whatsoever as to why a person of ordinary skill in the art would have opted to replace the hydrophobic proteins taught by Bernstein *et al.* with amphipathic proteins as recited in instant independent claim 1, or human serum albumin as recited independent claim 12 (and dependent claim 10). All of the embodiments described in the Bernstein *et al.* reference, as well as the emulsion methods used to make the microparticles, use hydrophobic proteins. Why one of ordinary skill in the art would opt to utilize an amphipatic protein such as human serum albumin is unclear, and unexplained by the Patent Office. As noted in the memorandum dated May 3, 2007 from Margaret A. Focarino to The Technology Center Directors in the wake of the *KSR v. Teleflex* decision ("Focarino Memo"; Exhibit 1):

> In formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.

Focarino Memo at page 2 (emphasis supplied).

Although there would have been so reason to do so, even if one were to combine the cited art in the manner combined by the Patent Office, the combination would fall short of the instantly claimed inventions. According to the Patent Office, it would have been obvious to one of ordinary skill in the are to "produce a multilayer particle comprising the polymers of Bichon *et al.* [and] to fill the core[s] of the microparticles with nitrogen ...," Office Action at page 4 (emphasis supplied). Layering "the polymers of Bichon *et al.*" as taught by Bernstein *et al.* would not yield microparticles having a hollow core, as recited in independent claims 1 and 12. The microspheres taught by Bernstein *et al.* are matrix particles that are solid. They do not have hollow cores. This is apparent from both the explicit definition of microspheres provided at page 7, lines 7-8 of the reference ("Microspheres are solid microparticles") and the emulsion methods used to make the microspheres. In addition, the disclosure related to incorporating

air teaches sonicating or agitating the protein solution before making the microspheres. Using the emulsion process described throughout the Bernstein *et al.* reference with a sonicated protein solution would yield substantially solid matrix microspheres having air entrapped throughout. It would not yield microparticles comprising a shell enclosing a gas filled hollow core as recited in independent claims 1 and 10.

Moreover, one of ordinary skill in the art would have had no reason to modify the multilayered particles of Bernstein *et al.* to include a hollow, gas-filled core. As plainly stated in the "Detailed Description of the Invention," the biodegradable protein microspheres of Bernstein *et al.* are used for *in vivo* release of biologically active agents incorporated therein "by diffusion from and/or degradation of, the microspheres," Bernstein *et al.* at page 4, lines 25-29. Altering the microspheres to include a gas-filled hollow core would do nothing to aid this purpose. Accordingly, one of ordinary skill in the art would have had no reason to modify the microspheres of Bernstein *et al.*, whether multilayered or not, to include a gas filled hollow core as recited in instant claims 1-8 and 10-16.

At a minimum, for a rejection under 35 USC § 103(a) based upon a combination of references to be proper, the references, when combined in the manner combined by the Patent Office, must teach each and every element of the rejected claims. The combination of cited art as applied by the Patent Office does not. Modifying the layered microspheres of Bernstein *et al.* to utilize the polymers of Bichon *et al.* would not yield microparticles comprising a shell enclosing a hollow gas-filled core as recited in claims 1-8 and 10-16.

It is noted that if the Bichon *et al.* reference were applied as the primary reference, the rejection would still fail. Assuming, *arguendo*, one of ordinary skill in the art were motivated to "coat" the synthetic polymeric microballoons of Bichon *et al.* with the proteins of Bernstein *et al.*, the outer layer of the membrane of the resultant microballoons would be composed of a hydrophobic protein, not an amphiphilic protein as recited in independent claim 1, or human serum albumin as recited in independent claim 12 and dependent claim 10.

Furthermore, one of ordinary skill in the art would have had no reason to combine the Bichon *et al.* and Bernstein *et al.* references. The references are directed to different problems. Bernstein *et al.* is directed to microspheres useful for *in vivo* controlled release of biologically active agents. Bichon *et al.* is directed to polymeric gas-filled microballoons useful for diagnostic imaging. And, as specifically noted by Bichon *et al.*, it is desirable to avoid the use of natural proteins such as albumins in the membranes of the microballoons:

> The great versatility in the selection of synthetic polymers is another advantage of the present invention since, as with allergic patients, one may wish to avoid using microballoons made of natural proteins (albumin, gelatin) . . .

Bichon *et al.* at Col. 9, lines 11-16 (emphasis supplied). Indeed, in the U.S. equivalent of the Bichon *et al.* reference mentioned by the Patent Office (U.S. Patent No. 5,840,275), proteins such as albumins are not even taught as being suitable polymers for making the microballoons.[2] Compare the relevant disclosures of the Bichon *et al.* reference with the corresponding disclosure of its U.S. equivalent '275 patent:

> The polymer which constitutes the envelope or bounding membrane of the injectable microballoons can be selected from most hydropholic, biodegradable physiologically compatible polymers. Among such polymers one can cite polysaccharides of low water solubility, polylactides and polyglycolides and their copolymers, copolymers of lactides and lactones such as ϵ-caprolactane, δ-valerolactone, polypeptides, and proteins such as gelatin, collagen, globulins and albumin.

Bernstein *et al.* at Col. 9, lines 2-11.

> The polymer which constitutes the envelope or bounding membrane of the injectable microballoons can be selected from most hydropholic, biodegradable physiologically compatible polymers. Among such polymers one can cite polysaccharides of low water solubility, polylactides and polyglycolides and their copolymers, copolymers of lactides and lactones such as ϵ-caprolactane, δ-valerolactone, polypeptides.

'275 patent at Col. 7, lines 32-39.

Thus, the Bichon *et al.* references specifically teaches against the use of natural proteins such as albumins in the membranes of its microballoons. One in the ordinary skill in the art would therefore not have had reason, and would have avoided, "coating" the synthetic polymeric microballoons of Bichon *et al.* with a natural amphiphilic protein such as human serum albumin.

Accordingly, for the reasons described above, it is submitted that the combination of references cited by the Patent Office does not render instant independent claims 1 and 10 obvious. Dependent

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[2] Other disadvantages of microballoons including heat-activated and cross-linked albumins are taught in the '275 patent at Col. 3, line 53 through Col. 4, line 17. *See also* U.S. Patent No. 6,177,062 to Stein *et al.* at Col. 1, lines 56-62 (Exhibit 2).

claims 2-8 and 11-16 are likewise non-obvious over the cited references for the same reasons. Withdrawal of the rejection is therefore requested.

While the various dependent claims are non-obvious for the same reasons as the independent claims 1 and 10, it is noted that dependent claims 15 and 16 are directed to embodiment of compositions in which the microparticles comprising the compositions do not contain a drug. The rejection as formulated by the Patent Office is inapposite to these claims. The primary reference, Bernstein *et al.*, is directed to protein microspheres useful for controlled release of biologically active agents *in vivo*. Such a reference has no bearing whatsoever on embodiments of compositions in which the microparticles do not include drugs, as recited in claims 15 and 16. Accordingly, the rejection does not apply to new claims 15 and 16.

NON-STATUTORY DOUBLE PATENTING

Claims 1-14 stand rejected under the judicially-created doctrine if obviousness-type double patenting as being unpatentable over claims 1-16, 19, 20 and 25-41 of U.S. Patent No. 6,193,951 to Ottoboni *et al.*, ("the '951 patent"); provisionally rejected under this same doctrine as being unpatentable over claims 1-27 of copending application Serial No. 10/977,100; and provisionally rejected under the same doctrine as being unpatentable over claims 3, 16-24 and 28-37 of copending application Serial No. 09/637,516 in view of the Bichon *et al.* reference.

A Terminal Disclaimer with respect to the '951 patent is enclosed herewith, obviating the non-statutory double patenting rejection over claims 1-16, 19, 20 and 25-41 of the '951 patent.

A Terminal Disclaimer with respect to any patent issuing on the '516 application is also enclosed, obviating the provisional rejection with respect to the claims of the copending '516 application.

Regarding the rejection over the claims of the '100 application, Applicant notes that the '100 application was filed on October 28, 2004, which is after the date on which the instant application was filed. Pursuant to MPEP Section 804(I)(B)(1), when a provisional double patenting rejection against a later-filed application is the only outstanding rejection in the earlier-filed application, and the later-filed application is still under rejection, the provisional double patenting rejection should be removed and the earlier-filed application permitted to issue. A review of PAIR indicates that to date, no Office Action has been mailed in the '100 application. Accordingly, it is requested that the provisional double patenting rejection over the claims of the '100 application be held in abeyance until such time as claims in the

instant application would be otherwise allowable, so that the Patent Office can then consider application of MPEP Section 804(I)(B)(1) to the instant application.

CONCLUSION

Claims 1-8 and 10-16 are believed to satisfy all of the criteria for patentability and are in condition for allowance. An early indication of the same is therefore kindly requested.

No fees beyond those specified in the accompanying documents are believed to be due in connection with this Amendment. However, the Director is authorized to charge any additional fees that may required, or credit any overpayment, to Dechert LLP Deposit Account No. 50-2778 (**Order No. 375430-002T1D1C1 (355479)**).

Respectfully submitted,

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